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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/071,826	02/08/2002	Mitchell F. Brin	17326CIP2 (BOT)	2841

51957 7590 12/28/2007

ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

EXAMINER	
HARRIS, ALANA M	

ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
12/28/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/071,826	BRIN ET AL.	
	Examiner	Art Unit	
	Alana M. Harris, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/02/2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11 and 34-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11 and 34-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments and Amendments

1. Claims 11 and 34-44 are pending.

Claims 36-44 have been added.

Claims 11 and 34-44 are examined on the merits.

Priority

2. Acknowledgment is made of applicants' claim for priority under 35 U.S.C. § 119(e). The Examiner has reviewed both, U.S. Application Serial No. 09/631,221, filed August 2, 2000 and U.S. Application Serial No. 09/454,842, filed December 7, 1999, now U.S. Patent number 6,139,845 from which priority is claimed. The limitations reading on atypical tissue and botulinum toxin implant are not disclosed in the priority documents. Thus, claims 11 and 34 will be granted the priority date of the instant application, February 8, 2002, as well as those claims that depend from the said claims. Applicants are reminded one claim is afforded one priority date, which represents the date at which all limitations are disclosed.

Claim Objections

3. Claim 35 is objected to because of the following informality: it depends from a cancelled claim 12. Correction is required.

New and Maintained Grounds of Rejection

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 11 and 35-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating a mammary gland disorder, which is an atypical tissue with botulinum toxin type A, does not reasonably provide enablement for preventing the development of an atypical tissue, thereby treating a mammary gland. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Applicants have set forth evidence supporting the treatment of mammary gland disorders (see specification beginning at page 45), however one of ordinary skill in the art cannot extrapolate these teachings enabling a method of preventing the development of an atypical tissue. It is known in the art that the term "atypical" describes in this particularly case, cells or tissues not typical, not corresponding to the normal form or type and often used to describe the appearance of precancerous or cancerous cells. The methodology listed in the specification is not commensurate in scope with claims, particularly the method of preventing any tumor growth in a mammalian host.

There is no guidance in the specification as to how to determine and select a population of individuals, which may or may not eventually have cancer. Preventing a disease is just as complex a process. It is not clear what parameters one skilled in the art would use in order to identify a population of subjects in which cancer could be prevented. It is also not clear what symptoms one of skill in the art would need to identify before possibly treating a patient. While it is art known that clinicians are capable of implementing both screening, surveillance and the type of screening test used and the intervals at which it is performed are based on risk stratification, which also serves as the basis for selecting potential candidates for possible prevention. However, like most screening procedures determining whether a population will eventually be struck with a disease is not fool proof.

Additionally, for methods that relate to the prevention of cancer, there is no guidance in the specification for determining the appropriate time prior to the development of tumors to begin the therapy or for identifying patients at risk for developing those tumors. Chamberlain (Expert Opinion on Pharmacotherapy, 1(4): 603-614, 2000) teaches that while vaccines are classically administered prophylactically to evoke an immune response capable of providing protection against infection by the same or similar pathogens for the treatment of infectious diseases, this has not been the approach in the field of cancer immunotherapy. Cancer is not an infectious process. Cancer cells express a limitless number of antigens and a priori knowledge of whom in the population is at risk for which cancer is lacking (see page 604, 1st column, first full paragraph). The specification provides insufficient guidance in regard to the issues

raised above and provides insufficient working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed methods in regard to all cancers with a reasonable expectation of success. In view of the above, one of skill in the art would be forced into undue experimentation to use botulinum toxin type A as a preventative composition.

There is insufficient evidence provided enabling one of ordinary skill in the art to determine susceptible cancer candidates within a population. The specification provides neither guidance on nor exemplification of identifying a population of people who may eventually have a tumor due to the presence of atypical tissue. Furthermore, if such a group was identified there is insufficient evidence provided that the tumor growth would be inhibited with the administration of botulinum toxin type A.

The criticality of a working example encompassing all of the method steps, especially the treatment of pre-existing neoplasia, is underscored by Gura et al. (Science 278: 1041-1042, November 7, 1997) in a discussion of potential shortcomings of extrapolating from animal studies to similar procedures in human cancer patients. Gura teaches that "xenograft tumors don't behave like naturally occurring tumors in humans" (page 1041, 2nd col, second full paragraph) and that there were "gross difference in sensitivity in real tumors in mice and in the clonogenic assay" (page 1042, second col, second full paragraph). Further, Gura teaches that clonogenic assays "cannot tell researchers how anticancer drugs will act in the body" (page 1042, first-second col, bridging paragraph). One skilled in the art would reasonably conclude that

evidence obtained in mouse xenograft models would not correlate with results expected in human patients.

Therefore, the complexity and unpredictability of the art to which the invention retains, i.e., *in vivo* human therapy, suggests the need for some guidance of how to effectively use the claimed methodology to achieve human therapeutic efficacy. There would also need to be some valid amount of direction or guidance, as well as presence or absence of working examples presented in the specification that would enable one skilled in the art to perform the method as presented in the recited claims. It appears that undue experimentation would be required of one skilled in the art to practice the instant claimed invention using the teachings of the specification. See Ex parte Forman, 230 USPQ 546 [BPAI, 1986].

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The rejection of claims 11, 34, 35 and newly added claims 36-38, 40-42 and 44 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent Application Publication 2001/0043930 A1 (effective filing date December 28, 1993), and further in view of Wald

and Kakulas (The Australian and New Zealand Journal of Surgery 33(3): 200-204, February 1964) is maintained and made.

Applicants' argue "[t]he [publication] discloses the treatment of conditions associated with muscle contraction and cholinergic controlled secretions", therefore "a skilled artisan would not be motivated...to use botulinum toxin to treat or prevent the development of atypical tissues", see Remarks submitted October 2, 2007, page 4, 3rd paragraph. Applicants assert the publication does not teach the development of atypical tissue and Wald does not "bridge the gap between the secretion of sweat,...and the development of atypical tissue.", see bridging paragraph of pages 4 and 5. In conclusion, Applicants further assert not to combine the teachings of Wald with teachings related to sweat glands and Wald teaches away from its combination with the publication, see last paragraph on page 5. These points of view and arguments have been carefully considered, but found unpersuasive.

While the publication does teach methods of treating muscle contractions and cholinergic controlled secretions this does not teach away from the publication's disclosure of treating mucus secretions. Wald does clearly cite"[a]pocrine glands are not sweat glands", see page 203, column 1, last paragraph. The Examiner does not disagree with Applicants on this citation, however within the same paragraph it is of record "[apocrine glands] elaborate a definite substance...". It is within the Examiner's purview the said substance is a mucus secretion. Hence, the combination of the two cited references is proper. The publication teaches the local administration of botulinum toxin type A to a patient suffering from a disease or conditions such as excessive

sweating, lacrimation and mucus secretions and Wald and Kakulas teach aprocrine gland carcinoma of the breast, which releases a substance, see publication's abstract; page 1, section 0014; page 2, section 0017; and page 4, Example 5; see Wald, page 203, column 1, last paragraph.

It would have been *prima facie* obvious to own of ordinary skill in the art at the time the invention was made to combine the teachings of the two documents because the publication teaches treating various disorders with botulinum toxins and suggests modifications can be made, see page 5, section 0069. One of ordinary skill in the art would have been motivated to treat apocrine gland carcinoma of the breast with botulinum toxin A using the designated dosages with a reasonable expectation of success by teachings well known in the art, because of the successful treatment of secretions and it is art known that dosages of any composition for treatment must be adjusted and optimized, see publication, page 2, sections 0026 and 0027; and page 4, section 0061. It is the Examiner's position intrinsic in the method of treating a mammary gland disorder with the botulinum toxin A there would be the reduction of the size of the neoplasm by at least 20% to about 100%. For the reasons of record and reiterated herein the rejection is maintained and made.

8. Claims 11 and 34-44 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent Application Publication 2001/0043930 A1 (effective filing date December 28, 1993), and further in view of Wald and Kakulas (The Australian and New Zealand Journal of Surgery 33(3): 200-204, February 1964) and U.S. Patent number 6,312,708

(filed July 21, 2000). The publication teaches the local administration of botulinum toxin type A to a patient suffering from a disease or conditions such as excessive sweating, lacrimation and mucus secretions, see abstract; page 1, section 0014; page 2, section 0017; and page 4, Example 5. The publication does not teach treating a mammary gland disorder with administration of the recited dosages in claims 11, 34, 37, 39 and 43 to the mammary gland and the implantation of a botulinum toxin implant.

However, Wald and Kakulas teach aprocrine gland carcinoma of the breast, which releases a substance, see page 203, column 1, last paragraph. The patent teaches a biodegradable polymer implant capable of releasing botulinum toxin A for various disease conditions, see column 16, lines 53-60. The patent also teaches the amount of botulinum A to be injected is generally between about 0.01 units per kilogram to about 35 units per kg, see bridging paragraphs of columns 25 and 26. It would have been *prima facie* obvious to own of ordinary skill in the art at the time the invention was made to combine the teachings of all of the documents because the publication teaches treating various disorders with botulinum toxins and suggests modifications can be made, see page 5, section 0069.

One of ordinary skill in the art would have been motivated to treat apocrine gland carcinoma of the breast with botulinum toxin A using the designated dosages with a reasonable expectation of success by teachings well known in the art, because of the successful treatment of secretions and it is art known that dosages of any composition for treatment must be adjusted and optimized, see publication, page 2, sections 0026 and 0027; and .page 4, section 0061. Moreover, one of ordinary skill in the art would

have motivated to do so with a reasonable expectation of success by teachings in all the references, that medical devices, such as implants are well known in the art for providing controlled or sustained release of pharmaceutical agents to treat disease.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

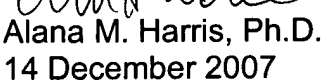
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (571)272-0831. The Examiner works a flexible schedule, however she can normally be reached between the hours of 7:30 am to 6:30 pm, with alternate Fridays off.

If attempts to reach the Examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ALANA M. HARRIS, PH.D.
PRIMARY EXAMINER



Alana M. Harris, Ph.D.
14 December 2007